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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,734	10/31/2003	Denise L. Faustman	00786/405003	3056

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/698,734	FAUSTMAN, DENISE L.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *13-29,31-44,47-52,58,61 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,30,45,46,53-57,59 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-62 are pending.

2. Applicant's election without traverse of Group I, claims 1-12, 30, 45, 46 and 53-62 and TNF-a receptor II agonist and diabetes as a specific disease as a in the reply filed on 12/27/06 is acknowledged.

Claims 13-29, 31-44, 47-52 (non-elected groups) and claims 58, 61 and 62 (non-elected species of elected group I) are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 1-12, 30, 45, 46, 53-57,59 and 60 read on a method for increasing or maintaining the number of functional cells of a predetermined type in an organ or tissue of mammal, comprising administering to said mammal a composition of enriched pluripotent cells that express the Hox 11 gene alone or in combination with administering TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances are under consideration in the instant application.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

4. The specification is objected to under 37 CFR 1.821(d) for failing to disclose SEQ ID NOS, for the nucleic acid sequence disclosed on page 28.

Applicant is reminded of the sequence rules which require a submission for all sequences of 10 or more nucleotides or 4 or more amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules.

Applicant is reminded to amend the specification accordingly.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 54 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 54 recites the limitation "blood cells" . There is insufficient antecedent basis for this limitation in the claim, since the base claims do not recites blood cells.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-12, 30, 45, 46, 53-57 , 59 and 60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification only discloses limited data obtained on NOD female mice wherein treatment with live splenocytes and CFA prolong survival of syngeneic islet graft and restoration of normoglycemia (see examples 1-4 and Table 1 and 2 in particular). Example 8 in the instant Specification is a prophetic examples that indicate what the inventor thinks might happen in the experiments which have not actually been performed.

The specification does not adequately teach how to effectively increasing or maintaining the number of any functional cells of any predetermined type in any organ or any tissue of any mammal, comprising administering to said mammal a composition of enriched pluripotent cells that express the Hox 11 gene alone or in combination with administering TNF-alpha or TNF-

alpha agonist or TNF-alpha inducing substances, as claimed in the instant claims. No animals models were used to study the effectively of increasing or maintaining the number of any functional cells of any predetermined type in any organ or any tissue of any mammal, comprising administering to said mammal a composition of enriched pluripotent cells that express the Hox 11 gene alone or in combination with administering TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances, as claimed in the instant claims.

Moreover, it is noted that in the disclosed examples the specification is relying on the data obtained in NOD mouse model.

Atkinson et al. ,(Nature, 1999, V.5, pages 601-604) teach that in addition to certain NOD strain-specific characteristics that distinguish these mice from humans at risk for type I diabetes important genus-specific features distinguish the murine diabetes as well, such as resistance to ketoacidosis or the absence of the murine homolog of HLA-DR molecules on APC. Investigators have not always considered that. Unfortunately, in a genetically heterogeneous human population containing individuals at high risk of type I diabetes development, there is little evidence that many of them would have a comparable set of immune deficiencies that prove as malleable. In NOD mice, type 1 diabetes development is well-choreographed. In contrast, the natural history of type 1 diabetes in human is such that the age of disease onset is extremely broad; symptoms occur at any time from the first years of life to well beyond 50 years of age. It is clear that the genus-unique and strain-specific aspects of diabetes in NOD mice must be fully understand and appreciated if we are to know which therapeutic protocols are reasonable to extrapolate to humans and which are not. Exploitation of the NOD genome for clinical research is yet to be done (see pages 602, 603 and 604 in particular).

It is noted that the Specification explicitly stated that even restoration of near normal pancreatic islet histology was observed only in diabetic NOD mice treated with CFA and received $\beta 2\ M^{-/-}$ allograft. Pancreatic islets were not detected in any diabetic NOD mice treated with CFA and syngeneic NOD islets. Kaufman et al., (J of Immunol. 1997, V.158, pages 2435-2442) teach that NOD mouse have been characterized to have a number of abnormalities in hematolymphopoiesis. The proportion of donor chimerism in NOD mice that initially repopulated as mixed chimeras tended to increase significantly over time to become predoninatly donor (see page 2438 in particular). Feldman et al (Transplant. Proc. 1998, 30, 4126-4127) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". Feldman et al . further teach that in a chronic immune-driven inflammatory response there are a number of pathways that become engaged and effective therapy in immune inflammatory diseases such as rheumatoid arthritis, will come from therapy aimed at several points in the disease pathway. Mestas et al (J. of Immunology, 2004, 172, pages 2731-238) teach that there exist significant differences between mice and humans in immune system development, activating and response to challenge in both the innate and adaptive arms. As therapies for human diseases become ever more sophisticated and specifically targeted it becomes increasing important to understand the potential limitations of extrapolating data from mice to humans. The

literature is littered with the examples of therapies that work well in mice but fail to provide similar efficacy in humans.

Moreover, an effective protocol for a method for increasing or maintaining the number of any functional cells of any predetermined type of any organ or any tissue is subject to a number of factors which enter the picture beyond simply the administration to the subject a composition of enriched pluripotent cells that express the Hox 11 gene alone or in combination with administering TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances, as claimed in the instant claims. Demonstrating prolong survival of syngeneic islet graft and restoration of normoglycemia in diabetic NOD mice after treatment with live splenocytes and CFA cannot alone support the predictability of a method for increasing or maintaining the number of any functional cells of any predetermined type of any organ or any tissue, by simply administering to a mammal a composition of enriched pluripotent cells that express the Hox 11 gene alone or in combination with administering TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances. Van Noort et al. (International Review of Cytology, 1998) indicate factors that effect immune response such as genetic, environmental and hormonal (Page 176, Paragraph 3). The ability of a host to enhance an immune response will vary depending upon factors such as the condition of the host and burden of disease.

Thus, since there is no animal model studies and data in the specification to show the effectively of the claimed method for increasing or maintaining the number of any functional cells of any predetermined type of any organ or any tissue comprising administration to the subject a composition of enriched pluripotent cells that express the Hox 11 gene alone or in combination with administering TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances, is unpredictable how one skilled in the art can practice the invention without an undue amount of experimentation. Therefore, it is not clear that the skilled artisan could predict the efficacy of a claimed method for increasing or maintaining the number of any functional cells of any predetermined type of any organ or any tissue. Thus in the absence of working examples or detailed guidance in the specification, the intended uses of the claimed method are fraught with uncertainties.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method for increasing or maintaining the number of any functional cells of any predetermined type of any organ or any tissue comprising administration to the subject a composition of enriched pluripotent cells that express the Hox 11 gene alone or in combination with administering TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-12, 30, 45, 46, 53-57 59 and 60 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 and 35-49 of co-pending Application NO:10/358,664. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-14 and 35- 49 of co-pending Application NO:10/358,664 recites a method of increasing or maintaining the number of functional cells of a predetermined type in a mammal, comprising administering pluripotent cells and TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 1-12, 30, 45, 46, 53-57 59 and 60 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6660487 or claims 1-18 of US Patent 6,599,710 . Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-15 of U.S. Patent No. 6660487 or claims 1-18 of US Patent 6,599,710 recites a method of increasing or maintaining the number of functional cells of a predetermined type in a mammal, comprising administering pluripotent cells and TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 571/273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MICHAIL BELYAVSKYI, PH.D.
PATENT EXAMINER
3/2/07